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Hormonal treatment and Quality of life of prostate cancer patients: new evidences

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Abstract

Androgen deprivation therapy (ADT) is the mainstay of treatment of patients with relapsed or metastatic hormone-sensitive prostatic carcinoma. The dramatic reduction of serum testosterone levels induced by ADT produces multiple side effects as vasomotor flushing, sexual dysfunction, fatigue, impairment of cognitive function, reduced quality of sleep, gynecomastia and anemia, that are able to decrease health-related quality of life (QoL). In addition, hormonal therapy can interfere with bone metabolism and induce metabolic and cardiovascular complications. Recently, new generation hormonal therapies, such as abiraterone and enzalutamide, have been tested and approved in castration resistant prostatic cancer patients and current studies are moving forward to the earlier use of these two drugs. In this evolving scenario, the management of hormonal therapy toxicity, given the long duration of treatment and the potentially high impact of side effects on patients' functional status and quality of life, is a critical challenge for clinicians. A correct information of patients before the initiation of treatment, together with the adoption of preventive measures, could help to ameliorate their quality of life. The aim of this review is to describe the impact on quality of life of endocrine treatment side effects and analyze possible interventions to alleviate them.

Keywords: prostate cancer, androgen deprivation therapy, enzalutamide, abiraterone, quality of life

Introduction

Prostate carcinoma is the second most common cancer and the second leading cause of cancer-related death among males in Western countries (1).

In patients with hormone-sensitive prostate cancer, testosterone is the main responsible of the growth of prostate cancer cells. Consequently, androgen deprivation therapy (ADT) represents the mainstay of treatment of patients with relapsed or metastatic hormone-sensitive disease (2).

The crucial role of ADT, either biochemical or surgical, as a therapeutic approach in this neoplasm has been established since the seminal work by Huggins and Hodges (3). ADT is able to reduce dramatically circulating testosterone levels, producing serological response (reduction in serum Prostate-Specific Antigen [PSA]) and clinical response in most patients (2).

According to clinical practice guidelines, ADT can be administered with potentially curative intent in association with radiation therapy in patients with localized disease but, unfortunately, this therapeutic option is not curative in metastatic setting (2). Despite the high probability of initial response, in fact, after a median time of 24-36 months, the disease becomes eventually resistant to ADT, with progression to the so-called phase of castration-resistance (4).

In recent years, due to a better understanding of prostate cancer biology and progression mechanisms, it has been clarified that the shift to castration-resistant prostate cancer is not induced by a true resistance to ADT, but rather to an adaptation of cancer cells, that acquire the ability to proliferate in a micro-environment characterized by low levels of testosterone (4,5).

Several data have shown that prostate cancer cells could synthesize their own androgens, and even small levels of androgens persisting despite castration could activate androgen receptor (AR) pathway (6). Multiple mechanisms are involved in this phenomenon, as upregulation of enzymes responsible of androgens production (4,5), AR gene mutation and overexpression (4,5), AR splice variants expression (4,5), increased synthesis of transcriptional co-activators (4,5).

According to these data, the AR pathway remains a key player also in castration-resistant prostate cancer (CRPC). This provided the rationale for the development of “new generation” hormonal therapies, as abiraterone acetate and enzalutamide (4,5).

Abiraterone acetate is an oral drug, able to potently inhibit the CYP17A1 enzyme, leading to a dramatic reduction in the production of testosterone, not only in testis but also in prostate cancer cells and adrenal glands (4,5).

Enzalutamide is an oral AR antagonist with 8-fold greater affinity to AR compared to first generation antiandrogen bicalutamide. In addition, enzalutamide prevents AR nuclear translocation and DNA binding (4,5).

In two phase III trials enrolling metastatic CRPC patients who had experienced disease progression after treatment with docetaxel, both abiraterone and enzalutamide showed a significant improvement in overall survival (OS) compared to placebo (7,8).

More recently, both abiraterone and enzalutamide demonstrated a significant improvement in survival also in asymptomatic or mildly symptomatic chemotherapy-naïve patients with metastatic castration resistant disease (9,10).

On the basis of these positive results, both U.S. Food and Drug Administration and European Medicines Agency approved abiraterone and enzalutamide for the treatment of

asymptomatic or mildly symptomatic chemotherapy-naïve CRPC patients and for the treatment of CRPC patients previously treated with docetaxel.

Both ADT and new generation hormonal therapies are effective and usually well-tolerated treatments for prostate cancer patients. However, many patients experience side effects that, although not causing treatment discontinuation, could significantly impair health-related quality of life (QoL). Indeed, managing the above-mentioned ADT-related morbidity is a key issue for prostate cancer patients, and an important challenge for their clinicians.

The aim of this review is to describe the impact of hormonal therapies side effects on QoL, and possible interventions to mitigate toxicity.

Androgen deprivation therapy and quality of life

ADT consists of different therapeutic options, which are able to induce a deep suppression of serum testosterone levels (11). These options include bilateral orchiectomy or medical castration achieved through the administration of luteinizing hormone releasing hormone (LHRH) analogues or antagonists (11). LHRH analogues induce an initial increase of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), as a consequence of stimulation of hypophysis receptors. Subsequently, chronic drug exposure is able to induce the hypophysis receptors down-regulation, causing the reduction of LH and FSH levels, and consequently of testosterone production (12).

On the contrary, LHRH antagonists block hypophysis receptors causing an immediate inhibition of testosterone synthesis, avoiding the initial, transient stimulation (13).

In recent years, the duration of hormonal treatment in prostate cancer patients has considerably expanded, due to a wider use of serum prostate-specific antigen (PSA) determination in clinical practice (14). Consequently, clinicians prescribe ADT also to many

patients with PSA increase alone after radical therapy, or to patients with limited metastatic disease. These patients have a low risk of disease progression and could be treated for a long time (14).

Shahinian and collaborators showed that ADT use increased progressively, during the 1990s, in a large cohort of more than 100,000 prostate cancer patients included in the Surveillance, Epidemiology and End Results-Medicare database, with different age, grades and stages of disease (15).

In this scenario, clinicians should pay more attention to the side effects associated with endocrine treatment than in the past.

The deep reduction of serum testosterone levels induced by ADT can cause several undesirable side effects as vasomotor flushing, loss of libido, erectile dysfunction, fatigue, reduced cognition and mood impairment, poor quality of sleep, gynecomastia and anemia, able to strongly interfere with QoL (16,17).

Additionally, prostate cancer patients treated with endocrine therapy are more likely doomed to develop osteoporosis (18), cardiovascular complications (14) and metabolic disorders such as decreased insulin sensitivity (14,17,19-23), diabetes (14,17,21), increase of cholesterol levels and fat body mass (14,17,21,22,24).

Several studies have documented an important reduction in QoL in prostate cancer patients treated with ADT (25-27). A study including men treated with adjuvant or salvage ADT post-prostatectomy showed a statistically significant reduction in seven QoL items (mental health and general health, energy, impact of cancer and treatment, concern regarding body image, activity, worries about cancer and dying) (28).

In a prospective study including 1642 patients with localized prostate carcinoma, treatment with ADT after three years of follow-up was able to decrease mental and physical health score, compared with controls (29).

Two randomized trials showed that hormonal therapy is able to induce a significant increase in emotional and cognitive impairment and an important reduction of libido and erectile function (27,30).

Dacal and collaborators studied the effects of ADT duration on QoL. They did not find significant differences between men treated with short term (< 6 months) compared with long term therapy (> 6 months) in terms of overall physical and global function (31).

Fatigue is one of the most important symptom affecting QoL in prostate carcinoma patients. It is not only caused by the disease itself, but it is frequently associated with hormonal therapy (14,17,24). In fact, the dramatic reduction of serum testosterone levels caused by ADT can induce anemia and a decrease in global functional status (14,16,17,24). Furthermore, several evidences showed that castration can generate important changes in body composition (25,32). Prostatic cancer patients treated with hormonal therapy have a high risk to develop a significant decrease of lean body mass, associated to a synchronous increase of overall body fat (25,32,33,34). The ADT-induced sarcopenia causes muscular weakness thereby contributing to development of fatigue (24).

Due to the loss of muscular strength and concomitant reduction of functional performance, prostate cancer patients treated with ADT have an increased risk of falls (35). This risk, in association with hormonal therapy-induced bone loss (25,35), favours the development of skeletal-related events (SREs). SREs are able to heavily interfere with QoL (35-38). Multiple studies demonstrated an increased risk of skeletal fractures among prostate cancer patients treated with hormonal therapy (36-38).

A higher incidence of depression has been described in men with decreasing serum testosterone (39). A recent meta-analysis including 18 studies and 168.756 men found that treatment with hormonal therapy is associated with an increased risk of depressive symptoms (40).

Fatigue and depression induced by ADT can interfere with cognitive function, producing a significant reduction in prostate cancer patients QoL (39,40).

In addition, observational studies found a positive correlation between serum testosterone and cognitive function (41). On the basis of these evidence, it is possible to hypothesize a direct negative effect of ADT on neurocognitive performance (41). In an observational study, Gonzalez and collaborators demonstrated that patients treated with ADT have a higher impairment of cognitive function compared with a control group including prostate carcinoma patients treated with surgery and men with no history of prostate cancer (42).

Impact of new generation hormonal therapies on quality of life

Following the demonstration of efficacy of abiraterone and enzalutamide in CRPC patients, that inform the use of these agents in current clinical practice, ongoing studies are moving forward to the use of these two drugs in an earlier phase of disease.

Two trials have explored the efficacy of enzalutamide in association with ADT compared to bicalutamide plus ADT. The TERRAIN trial is a phase II study that randomized 375 metastatic CRPC patients progressing on ADT to enzalutamide 160 mg daily plus ADT or bicalutamide 50 mg daily plus ADT. Enzalutamide-treated patients demonstrated an increase of nearly 10 months in median progression-free survival (15.7 vs 5.8 months) compared to bicalutamide arm (HR: 0.44; 95% CI 0.34–0.57; $p < 0.0001$) (43). STRIVE trial is a double-blind phase II study that enrolled 396 men with metastatic or non-metastatic

CRPC, randomized to enzalutamide 160 mg per day plus ADT or bicalutamide 50 mg per day plus ADT. Treatment with enzalutamide significantly improved progression-free survival compared with bicalutamide (median 19.4 vs 5.7 months; HR: 0.24; 95% CI: 0.18–0.32; $p < 0.001$) (44).

All the main trials involving Enzalutamide and Abiraterone Acetate provided analysis based on patient-reported outcomes (PROs). PROs are increasingly taken in consideration by clinicians when approaching new drugs in clinical trials. PROs guarantee more accuracy in defining patients' symptoms compared to clinicians reports (45-46). In the future, PROs may possibly be integrated into everyday clinical practice, improving cancer patients' QoL, as it has been proved in a single-centre randomized trial (47). The most widely used questionnaires for assessment of PROs are the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire and the Brief Pain Inventory Short Form (BPI-SF).

Abiraterone was found to delay the FACT-P score deterioration when compared to placebo, in both post-chemotherapy and pre-chemotherapy settings (48). Abiraterone also proved to decrease the time to worst pain intensity palliation, defined as two consecutive follow-up visits (≥ 4 weeks apart) at which the worst pain intensity score was $\geq 30\%$ lower than baseline, without an increase in analgesic use, in patients already treated with docetaxel (COU-AA-301). Pain interference palliation, defined as a decrease in mean pain interference score of ≥ 1.25 points compared with baseline at two consecutive follow-up visits, was improved in the abiraterone group compared to placebo group. In the COU-AA-302 trial (pre-docetaxel setting) a similar impact of abiraterone in pain palliation could not be proved, because, at baseline, 69% of patients in the abiraterone group and 65% of placebo group were asymptomatic, and many of the patients enrolled did not use analgesics. However, abiraterone showed to prolong the time to progression of mean and worst pain

intensity (26.7 vs. 18.4 and 26.7 vs. 19.4 months for abiraterone and placebo, respectively).

Indeed, even for mCRPC patients who are minimally symptomatic or asymptomatic, there is an expected delay in the deterioration of quality of life or delayed cancer-related symptoms.

PROs of patients enrolled in trials conducted with enzalutamide were summarized in a recent review, that considered data of four studies: AFFIRM, PREVAIL, STRIVE, and TERRAIN (49). There was a significant difference in QoL improvement, defined as a 10-point improvement on two consecutive measurements at least 3 weeks apart (a commonly accepted definition of response in FACT-P), between patients treated with enzalutamide and patients receiving placebo in the post-docetaxel settings (AFFIRM). In the PREVAIL and TERRAIN trials, conducted in the pre-docetaxel setting, enzalutamide proved to delay time to degradation of FACT-P, defined as a 10-point decrease from baseline score (without requirement for confirmation in a subsequent measurement), when compared to placebo and bicalutamide, respectively. On the other side, no differences were observed in the STRIVE trial between the enzalutamide and bicalutamide groups. The trial did not report how often FACT-P was obtained or the percentage of patients who were included in the analysis. In the AFFIRM and PREVAIL trials, investigators used BPI-SF scale to assess the impact of enzalutamide on pain progression. Fewer patients had pain progression in the enzalutamide group than in the control group, mainly in the first evaluation after baseline (week 13).

The Cog-Pro study is an ongoing multicentre longitudinal study including CRPC patients older than 70, treated with new-generation hormonal therapies. The study aims to add an important evaluation, as the incidence of cognitive impairment in elderly men treated with enzalutamide and abiraterone has not been yet specifically investigated. Objective cognitive function will be evaluated by the International Cognition and Cancer Taskforce recommended battery of tests, performed by a neuropsychologist. Validated self-report

questionnaires will be used to investigate secondary endpoints, including fatigue, cognitive complaints, depression, anxiety, and quality of sleep, as well as general and specific functional assessment of Cancer Therapy (FACT-G, FACT-P) for QoL. This study should help to improve cancer care of elderly patients (50).

Preventive interventions for hormonal therapy side effects

Lifestyle changes, such as increased physical exercise and dietary corrections, have been considered in several studies with the purpose of improving patient-reported outcomes. Two recent systematic reviews evaluated the results of randomized controlled trials (RCTs) that investigated the impact of lifestyle interventions in patients with prostate cancer. Menichetti et al. included 17 RCTs, involving a total of 1989 patients with prostate cancer (51). However, less than half the patients (47%) were undergoing ADT. Exercise studies, in particular supervised resistance training programs, yielded the greater amount of positive results on QoL (67%, 8 out of 12), followed by dietary interventions (50%, 1 out of 2) and combined lifestyle interventions (33%, 1 out of 3). In the reviews' conclusions, authors underline the lack of methodological quality among the RCTs included in the review, and affirm that additional large-scale RCTs with low bias risk are needed to better define the benefits of lifestyle interventions in ameliorating QoL of prostatic cancer patients. Teleni et al. collected data reported by 9 RCTs (16). All patients included in the trials were undergoing ADT. Seven RCTs investigated the effects of exercise over 12-24 weeks on QoL, using either health-related QoL (5 trials) or disease-specific QoL (2) tools. Physical activity was associated with significant improvements of QoL, regardless the outcome measures used to assess quality of life. However, the effect was small to moderate in the clinical magnitude and no trials proved that exercise significantly improve metabolic risk

factors, such as total body weight, body composition, as measured by dual-energy X-ray absorptiometry (DXA), and systolic blood pressure. Moreover, the majority of RCTs implemented resistance and aerobic exercise as combined intervention, so that it is not possible to quantify the efficacy of each type. The review included two dietary RCTs that investigated the efficacy of 12 weeks of soy supplementation, finding no differences between the experimental and observational arm for primary and secondary outcomes.

The authors of the two reviews agree to attribute the variability of results obtained by different RCTs to the heterogeneity in the design of the studies included. In particular, the logistical inability to blind participants, the difficulty to evaluate the compliance of patients in the experimental arms, and the usage of different outcome measures were addressed to be the major criticisms. Moreover, identifying patients that are more likely to have a significant decrease in QoL from ADT and that may benefit most from preventive interventions, may be quite a challenge in the clinical practice. Indeed, all the tools used for the prediction of clinical outcomes in patients with prostatic cancer failed to adequately predict PROs (52).

Although the impact of physical activity in ADT-treated patients is not yet clear, ESMO guidelines strongly recommends that “men starting ADT should be informed that regular exercise reduces fatigue and improves quality of life” (53).

Conclusions

The “proactive” management of adverse events and symptoms, based on the use of patient reported outcomes, allows a significant benefit in terms of patients’ quality of life, and this should favour the adoption of PROs in clinical practice (54). Hormonal treatment plays a crucial role in the treatment of patients with prostate cancer, who can receive ADT, or new generation drugs, even for many years. Given this long duration of treatment, and the

potentially high impact of side effects on patients' functional status and quality of life, it is mandatory that physicians pay attention to the diagnosis and management of side-effects. A correct information of patients before the initiation of treatment, together with the adoption of preventive measures, could help to ameliorate their quality of life. Considered the high prevalence of the disease, and the clinical relevance of the endpoints, clinical research in this field should be strongly encouraged.

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